REMARKS

The Office Action of November 3, 2005 has been received and reviewed. Claims 1 - 27 and 47 were previously cancelled herein without prejudice or disclaimer. Claims 28, 40, 48, and 49 have been amended herein without prejudice or disclaimer. Claim 55 has been added. Claims 40, 43, and 50-54 have been withdrawn by the Examiner. All of the pending claims 28-46 and 48-55 are presented herein and stand rejected. Reconsideration is respectfully requested.

The amendment to claim 28 was made to correct typographical errors and to rewrite the word 'optionally' more appropriate to Office practice. The amendment did not surrender any claim scope.

Support for claim 55 can be found in original claim 28. New claim 55 reads on the elected species and is within the elected group.

Remarks to the Examiner's Response to Restriction and Election of Species

The Examiner states in paragraph 5 of the Office Action that claims 40, 43, and 50-54 are withdrawn from consideration. The Examiner withdrew claims 50-54 because Applicants allegedly stated that the claims did not read on the elected species. However, in the Response to the Non-Responsive Amendment Notice of June 10, 2005, filed on or about July 7, 2005, Applicants stated, on page 7, that claim 50 does not read on the elected species and that claims 51-54 do read on the elected species. Accordingly, claims 51-54 should not have been withdrawn by the Examiner and Applicants respectfully request reconsideration, rejoinder, and examination of at least claims 51-54.

Remarks to Restriction and Election of Species

Applicants extend their thanks to the Examiner for withdrawing the subgroup 4 species election.

Information Disclosure Statement

Applicants are submitting a Supplemental Information Disclosure Statement (IDS) correcting alleged defects in the citations noted by the Examiner. Copies of the documents have

previously been submitted. Accordingly, Applicants are not submitting further copies. As the IDS is being submitted after the First Office Action on the merits, but prior to the mailing of a Final Rejection or Notice of Allowance, Applicants are paying the required fee.

Priority

Applicants have amended the priority paragraph in conformance with the Examiner's suggestion, noting that the filing was as a divisional of copending USSN 10/199,805, filed July 19, 2002, now abandoned, and respectfully request reconsideration and withdrawal of the objection.

Claim Objections

Claim 48 stands objected as allegedly being a substantial duplicate of claim 28. The Examiner contends that the term "automated" in claim 48, "[a] method for automated solution synthesis of peptides, wherein the process of claim 28 is applied", is not accorded any patentable weight. Applicants respectfully request reconsideration in light of the amendment to claim 48 and the following response.

While not agreeing with the Examiner, Applicants have amended claim 48. Claim 48 now recites "[t]he process of claim 28, said process applied in a method for automated solution synthesis of peptides." Amended claim 48 depends on claim 28 and adds the element of a method for automated solution synthesis of peptides. Accordingly, amended claim 48 is believed to add patentable weight that does not depend upon the preamble for completeness. Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim 28 has been amended to overcome the objection, thereby mooting the objection.

Rejections under 35 USC §102(b)

Claims 28, 30, 31, 36, 41, 42, 44-46, 48, and 49 stand rejected under 35 USC §102(b) as allegedly being anticipated by a 1999 article to Carpino ("Carpino") as allegedly evidenced by a Solomons publication (Solomons, T.W.G. Organic Chemistry Fifth Edition. New York: John

Wiley & Sons. 1992, page 94, Table 3.1) ("Solomons"). Applicants respectfully request reconsideration in light of the Declaration of Ivo Eggen and the following response.

Carpino discloses a process for the production of peptides containing more than one cycle and each cycle containing a coupling step, a quenching step and an extraction step. Carpino does not disclose a process comprising at least one cycle with a step in which an amine comprising a free anion or a latent anion is used as a scavenger of residual activated carboxylic functions. The Examiner contends that Carpino discloses the use of ethanolamine as a scavenger on page 4329, column 1, first paragraph. Further, the Examiner contends that Carpino would have inherently had the property of an amine comprising a free anion or a latent anion. The Examiner bases this contention on the assumption that ethanolamine in water would be present in a deprotonated form. However, this assumption is incorrect because the hydroxy function of ethanolamine is less acidic than water. Accordingly, ethanolamine is not deprotonated in an aqueous solution. Therefore, the function is not deprotonated during aqueous extractions. Consequently, it does not form an anion under the conditions as used and disclosed by Carpino.

The alcohol function of ethanolamine is deprotonated using a very strong base, such as, for example, by potassium hydride, in a non-aqueous solvent. Such conditions are incompatible with peptide synthesis involving aqueous conditions.

In the Declaration of Ivo Eggen ("the Eggen Declaration"), differences in embodiments of the claims 28, 30, 31, 36, 41, 42, 44-46, 48, and 49 in comparison with the Carpino process are discussed. Ivo Eggen ("Eggen") is employed as a chemist by Diosynth B.V., Oss, the Netherlands, as Senior Project Manager Peptides. He is also a co-inventor of the present application and a declarant in this response. (See, the Eggen Declaration, ¶2 and 3). As a peptide chemist, with over ten years experience, Eggen is also familiar with Carpino and Solomons. (See, the Eggen Declaration, ¶4).

Eggen helped discover and develop a process termed DioRaSSP® (Diosynth Rapid Solution Synthesis of Peptides). DioRaSSP® is a method for the solution-phase synthesis of peptides that differs from other known processes, such as the process disclosed in Carpino. Claims 28-46 and 48-54 were drafted to claim various embodiments of the DioRaSSP® process.

Using the DioRaSSP® process, the growing peptide is essentially anchored in a permanent organic phase, by means of its hydrophobic C-terminal and side-chain protecting groups. (See, the Eggen Declaration, ¶6). As shown in Figure 1 to the Exhibit of the Eggen Declaration, one cycle of an embodiment of the DioRaSSP® process consists of a coupling step, scavenging of residual activated carboxylic compound, aqueous extractive work-up, deprotection of the N-terminal amino function, and finally another aqueous extractive work-up. Couplings are mediated by water-soluble carbodiimide to allow aqueous extractive work-up and avoid an additional filtration step. (See, the Eggen Declaration, ¶6). Claim 28 has as elements steps (a)-(c); wherein (a) comprises a coupling step, using an excess of a molecule comprising an activated carboxylic to acylate an amino component, wherein (b) comprises a quenching step in which a scavenger is used to remove residual activated carboxylic functions, wherein the scavenger may also be used for deprotection of the growing peptide, and wherein (c) comprises one or more aqueous extractions, wherein the process comprises at least one step (b), referred to as step (b'), in which an amine comprising a free anion or a latent anion is used as a scavenger of residual activated carboxylic functions. A new claim 55 has been added to further claim step (d), a separate deprotection step, followed by one or more aqueous extractions. Accordingly, elements of claim 28 are an embodiment of the DioRaSSP® process.

In claim 28, after completion of a coupling, residual activated carboxylic compound, if hydrophobic, is scavenged with a compound containing a nucleophilic moiety (*e.g.,* an amine), which is able to convert an activated carboxylic moiety, as well as an anion-forming moiety, which can be deprotonated under mildly basic aqueous conditions compatible with peptide synthesis. Thus, the DioRaSSP® process, and claim 28, assures the quantitative removal of scavenged compounds before the coupling step of the next cycle of the synthesis by basic aqueous extraction, while the growing peptide remains anchored in the organic phase due to the presence of hydrophobic protecting functions. (See, the Eggen Declaration, ¶7).

A repetitive method for peptide synthesis is disclosed in Carpino. Carpino reported the use of a(n) (poly)amine as a scavenger for residual activated carboxylic compounds in addition to the application of the group 1,1-dioxobenzo[*b*]thiophene-2-ylmethoxycarbonyl (Bsmoc) as amino-protecting in the process. The Bsmoc function has very high lability towards base. As a

result, in one step residual activated carboxylic functions are scavenged and Bsmoc functions are removed using a(n) (poly)amine. Thus, in the Carpino process, deprotection of the N-terminal function necessarily takes place under the same reaction conditions as the scavenging of excess activated carboxylic functions. (See, the Eggen Declaration, ¶8).

Further, Carpino discloses experiments performed to gain a general picture of the ease of the deblocking process, using a number of simple deblocking amines. The following reactivity order was observed: piperidine > piperazine > morpholine ≈ ethanolamine. The lowest reactivity rate was observed with the primary amine ethanolamine. (See, the Eggen Declaration, ¶9).

It is known and published in Solomons that ethanolamine in water is present in the non-dissociated form $NH_2CH_2CH_2OH$, the pK_a of water being lower (15.74) than that of ethanolamine (16) (See, Solomons). Accordingly, in water, the alcohol function of ethanolamine cannot be deprotonated, as the hydrogen in the hydroxy group of ethanolamine is less acidic than the hydrogen of the water molecules. The alcohol function of ethanolamine can only be deprotonated using a very strong base, such as potassium hydride, in non-aqueous solvents. Such conditions are incompatible with peptide synthesis involving aqueous conditions. (See, the Eggen Declaration, ¶10).

Further, the various scavengers disclosed by Carpino are different from the scavengers used in various embodiments of the present application. Scavengers disclosed in various embodiments of the present application comprise an anion-forming moiety, which can be deprotonated under mildly basic aqueous conditions compatible with peptide synthesis, whereas the scavengers used and disclosed by Carpino do not comprise such a moiety. (See, the Eggen Declaration, ¶11). One of ordinary skill in the art would recognize that in the solution synthesis of peptides according to Carpino, the alcohol functionality of ethanolamine remains intact during aqueous washings and does not form an anion. (See, the Eggen Declaration, ¶12). Accordingly, Carpino does not disclose the processes claimed in Claims 28, 30, 31, 36, 41, 42, 44-46, 48, and 49. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejections Under 35 USC §103(a)

Claims 28-31, 36, 41, 42, 44-46, 48, and 49 stand rejected under 35 USC§103(a) as allegedly being unpatentable over Carpino, WO 2000/71569 ("the '569 publication"), and a 1991 article to Houghten et al. (Houghten et al. "Generation and use of synthetic peptide combinatorial libraries for basic research and drug discovery" ***Nature***, 354, 84-86 (1991)) ("Houghten").

The Examiner bases the rejection of claims 28, 30, 31, 36, 41, 42, 44-46, 48, and 49 on the §102(b) rejection by stating that because the claims are anticipated, the claims are rendered obvious as well. Therefore, the previous analysis with respect to the §102(b) rejection applies equally as well to the instant rejection. Accordingly, as Carpino does not anticipate claims 28, 30, 31, 36, 41, 42, 44-46, 48, and 49, Carpino cannot render the claims obvious. Applicants respectfully request reconsideration and withdrawal of the rejection.

As claim 29 depends upon claim 28, and the elements of claim 28 are not taught or disclosed by Carpino, all elements of claim 29 are not taught or disclosed by the combination of Carpino, the '569 publication and Houghten. Applicants respectfully request reconsideration and withdrawal of the rejection.

As amended claim 48 depends upon claim 28 and the elements of claim 28 are not taught or disclosed by Carpino, all elements of amended claim 48 are not taught or disclosed by the combination of Carpino, the '569 publication and Houghten. Applicants respectfully request reconsideration and withdrawal of the rejection.

Double Patenting Rejection

Claims 28-39, 42, 44-46, 48, and 49 stand provisionally rejected under 35 USC §101 as allegedly claiming the same invention as claims 28-39, 42, 46-48, 50, and 51 of co-pending Application 10/692,354, published as 2004/0082760 A1 ("the '354 application"). As this is a provisional rejection, Applicants respectfully request that the rejection be held in abeyance until at least one set of the claims is indicated as allowable. Upon an indication of allowability, Applicants will address, as needed, the same invention type double patenting rejection.

Claim 41 stands provisionally rejected under the judicially created doctrine of

obviousness type double patenting as allegedly being unpatentable over claim 41 of the '354 application. As this is a provisional rejection, Applicants respectfully request that it be held in abeyance until at least one of the claims is indicated as allowable. Upon an indication of allowability, Applicants will address, as needed, the obviousness type double patenting rejection.

Claims 28-39, 41, 42, 44-46, 48, and 49 stand rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 1-14 of US 6,864,357 (hereinafter referred to as the '357 patent). While not agreeing with the Examiner, to further prosecution of the case, Applicants are filing a terminal disclaimer in the present case disclaiming the terminal portion of the term of the any claim issuing from the present application that would extend beyond that of the '357 patent.

CONCLUSION

If questions remain after consideration of the foregoing, the Office is kindly requested to contact Applicants' attorney at the address or telephone number given herein.

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